AMENDMENTS TO THE SPECIFICATION:

Please replace paragraph 0002 with the following amended paragraph:

[0002] The present invention relates to the use of a microorganism or cell containing a DNA sequence encoding a detectable protein or a protein capable of inducing a detectable signal, e.g. a luminescent or fluorescent protein, for the preparation of a diagnostic composition for diagnosis and/or visualization of wounded or inflamed tissue or a disease associated therewith. The present invention also relates to therapeutic uses wherein said microorganism or cell additionally ~~contain~~ contains an expressible DNA sequence encoding a protein suitable for therapy, e.g. an enzyme causing cell death or digestion of debris.

Please replace paragraph 0005 with the following amended paragraph:

[0005] A number of investigators have focused on the nature of the implanted materials as the factor that influences the ability of bacteria to adhere. Materials such as sutures and surgical clips which are used for closure of wounds, are potential sites of bacterial colonization. Infection of these materials may impede wound healing and/or place patients at increased risk of secondary infections. A variety of wound closure materials have been manufactured with varying affinities for bacteria. Certain wound closure materials, such as braided sutures, have been associated with a higher incidence of infection. The multifilament nature of this type of suture material lends itself to increased susceptibility to bacterial colonization as well as causing a wicking effect that allows penetration of bacteria across the tissues. [[Mere]] More permanent implantable materials have demonstrated a similar affinity for bacteria. Prosthetic heart valves and joints may be at increased risk of bacterial colonization. It is commonly believed that this higher susceptibility is caused by the inherent ability of bacteria to adhere more readily to the implant surfaces. An alternative explanation may be that inflammation in the tissues surrounding the implants provides an environment that is more suitable for bacterial colonization. In addition to these given possibilities, another factor that may influence the susceptibility of a site, with regards to colonization with bacteria could be the degree of inflammatory status of the affected tissues. Implanted materials may create transient or chronic sites of inflammation in the body.

Please replace paragraph 0006 with the following amended paragraph:

[0006] Presence of implanted materials is not a requirement for bacterial colonization. Alteration of natural anatomical structures that may arise from disease conditions may produce surfaces that are easier to colonize by bacteria. It had been suggested that for the occurrence of infective endocarditis [[(E),]](IE), the valve surface must be altered in order to produce a suitable site for bacterial attachment and colonization. Additionally, the microorganisms have to reach this site and adhere, since it is not possible to produce IE in experimental animals with injections of bacteria unless the valvular surface is damaged. Lesions with high turbulence create conditions that lead to bacterial colonization, whereas defects with a large surface area or low flow are seldom implicated in IE.

Please replace paragraph 0020 with the following amended paragraph:

[0020] Intravenous injection of the rats with $1X10^8$ attenuated E. coli transformed with the plasmid pLITE201 carrying the ~~luxedabe~~ luxcdabe operon did not lead to colonization of the hearts of control animals, which had not been catheterized (A). Similar induction of bacteremias in rats catheterized through the right carotid artery lead to the colonization of the heart with light emitting bacteria (B).

Please replace paragraph 0025 with the following amended paragraph:

[0025] The present invention also relates to the use of a microorganism or cell containing a DNA sequence encoding a detectable protein or a protein capable of inducing a detectable signal for the preparation of a pharmaceutical composition for the treatment of wounded or inflamed tissue or a disease associated therewith, wherein said ~~micoroorganism~~ microorganism or cell furthermore contains one or more expressible DNA sequences encoding (a) protein(s) suitable for the therapy of wounded or inflamed tissue or diseases associated therewith.

Please replace paragraph 0034 with the following amended paragraph:

[0034] Luciferase genes have been expressed in a variety of organisms. Promoter activation based on light emission, using luxAB fused to the nitrogenase promoter, was demonstrated in Rhizobia residing within the cytoplasm of cells of infected root nodules by low light imaging (Legocki et al., PNAS 83 (1986), 9080-9084; O'Kane et al., J. Plant Mol. Biol. 10 (1988), 387-399). Fusion of the lux A and lux B genes resulted in a fully functional luciferase protein (Escher et al., PNAS 86 (1989), 6528-6532). This fusion gene (Fab2) was introduced into

Bacillus subtilis and Bacillus megatherium under the xylose promoter and then fed into insect larvae and was injected into the hemolymph of worms. Imaging of light emission was conducted using a low light video camera. The movement and localization of pathogenic bacteria in transgenic arabidopsis plants, which carry the pathogen-activated PAL promoter-bacterial luciferase fusion gene construct, was demonstrated by localizing Pseudomonas or ~~Ervinia~~ Erwinia spp. infection under the low light imager as well as in tomato plant and stacks of potatoes (Giacomin and Szalay, Plant Sci. 116 (1996), 59-72).

Please replace paragraph 0045 with the following amended paragraph:

[0045] For administration, the microorganisms or cells described above are preferably combined with suitable pharmaceutical carriers. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc.. Such carriers can be formulated by conventional methods and can be administered to the subject at a suitable dose. Administration of the microorganisms or cells may be effected by different ways, e.g. by intravenous, ~~intraperetoneal,~~ intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration. The preferred route of administration is intravenous injection. The route of administration, of course, depends on the nature of the tissue and the kind of microorganisms or cells contained in the pharmaceutical composition. The dosage regimen will be determined by the attending physician and other clinical factors. As is well known in the medical arts, dosages for any one patient depends on many factors, including the patient's size, body surface area, age, sex, the particular compound to be administered, time and route of administration, the kind and localisation of the tissue, general health and other drugs being administered concurrently.

Please replace paragraph 0046 with the following amended paragraph:

[0046] A preferred ~~therapeutical~~ therapeutic use is the preparation of a pharmaceutical composition for the treatment of endocarditis, pericarditis, inflammatory bowel disease (e.g. Crohn's disease or Ulcerative colitis), low back pain (herniated nucleus pulposis), temporal arteritis, polyarteritis nodosa or an arthritic disease.

Please replace paragraph 0047 with the following amended paragraph:

[0047] In the past few years, there [[has]] have been many reports showing evidence for Chlamydia pneumoniae, ~~Heliobacter~~ Helicobacter pylori, CMV, HSV and other infectious agents inside atherosclerotic plaques. The presence of these infectious agents within atherosclerotic plaque suggests that the interior of the plaque is a protected environment that permits replication, otherwise these infectious agents would be cleared by the immune system. Moreover, there is considerable evidence that an inflammatory process is present within the interior of atherosclerotic plaque. Accordingly, it is reasonable to assume that this disease can be diagnosed and treated by the microorganisms or cells of the present invention that after intravenous injection--will penetrate into the atherosclerotic plaque where they start to replicate. After a suitable period of time, the plaque can be imaged using, e.g., light sensitive cameras or suitable MRI equipment. Further, said microorganisms or cells can additionally produce an enzyme, e.g. an enzyme as described above, resulting in the elimination of plaques. Thus, a further preferred use is the diagnosis and treatment of an atherosclerotic disease.

Please replace paragraph 0057 with the following amended paragraph:

[0057] Five- to six-week-old male BALB/c nu/nu mice (25-30 g body weight) and Sprague Dawley rats (300-325 g body weight) were purchased from Harlan (Frederick, Md., U.S.A.). ~~CS7BL/6J~~ C57BL/6J mice were obtained from Jackson Laboratories (Bar Harbor, Me., U.S.A.). All animal experiments were carried out in accordance with protocols approved by the [[Lorna]] Loma Linda University animal research committee. The animals containing recombinant DNA materials and attenuated pathogens were kept in the Loma Linda University animal care facility at biosafety level two.

Please replace paragraph 0060 with the following amended paragraph:

[0060] To determine the fate of intravenously injected luminescent bacteria in the animals, $1X10^7$ bacteria carrying the pLITE201 plasmid DNA in [[50 il]] 50 µl were injected into the left femoral vein of nude mice under anesthesia. To expose the femoral vein, a 1-cm incision was made with a surgical blade. Following closure of the incision with 6-0 sutures, the mice were monitored under the low light imager and photon emissions were collected for one minute. Imaging of each animal was repeated at various time intervals to study the dissemination of the light-emitting bacteria throughout the body of the animals. It was found that the

distribution pattern of light emission following an intravenous injection of bacteria into the mice was bacterial-strain-dependent. Injection of attenuated S. typhimurium caused wide dissemination of the bacteria throughout the body of the animals (FIG. 1A). This pattern of distribution was visible within 5 minutes after bacterial injection and continued to be detected at the one-hour observation period. Injection of attenuated V. cholera into the bloodstream, however, resulted in light emission that was localized to the liver within 5 minutes after bacterial injection and remained visible in the liver at the one-hour observation period (FIG. 1B).

Please replace paragraph 0061 with the following amended paragraph:

[0061] The difference in the bacterial distribution patterns suggests a difference in the interaction of these strains with the host once inside the animal. Imaging the same animals 48 h after bacterial injection showed that all of the detectable light emission from the earlier time had diminished and was eliminated completely from the injected animal with the exception of the inflamed wounded tissues such as the incision wound and the ear tag region. Inflammation in these tissues was identified by their red and edematous appearance. Light emission was detected in the incision wound and/or in the inflamed ear tag region up to 5 to 8 days post injection, which was confirmed by longer photon collection times, i.e. 10 minutes (FIG. 2A-C and FIG. 3A-C). The absence of light emission was not due to the loss of the plasmid DNA or the silencing of gene expression in the bacteria. In other experiments light emission in animals could be consistently detected for up to 50 days. Similar data were obtained in immunocompetent ~~C57BU6J~~ C57BL/6J mice (FIG. 4), showing that these observations are not limited to animals with altered immune systems. Careful examination of individually excised organs as well as blood samples from infected animals confirmed the absence of luminescence in these normal uninjured tissues. Furthermore, the experimental data demonstrated that colonization of the injured tissues is a common occurrence in mice. Twenty-four of 29 incision wounds (82.8%) and 12 of 29 ear tags (41.4%) in the mice were colonized by intravenously injected bacteria. Wound colonization by intravenously injected bacteria occurred following injection of V cholera in concentrations as low as $1X10^5$ bacterial cells.

Please replace paragraph 0062 with the following amended paragraph:

[0062] Surgical heart defects were created according to the procedures previously described (Santoro and Levison, Infect. Immun. 19(3) (1978), 915-918; Overholser et al., J. Infect. Dis. 155(1) (1987), 107-112). Briefly, animals were anesthetized with sodium pentobarbital (60 mg/kg i.p.). A midline neck incision was made to expose the [[tight]] right carotid artery. A polypropylene catheter was introduced and advanced until resistance was met indicating insertion to the level of the aortic valve. The catheter was then secured using a 10-0 suture (AROSurgical Instrument Corporation, Japan) and the incision was closed using 4-0 silk sutures (American Cyanamide Company, Wayne, N.J.). Placement of the catheter causes irritation and subsequent inflammation of the aortic valve (Santoro and Levison, 1978). Control animals did not undergo the catheterization procedure. Bacteremias were induced by injection of $1X10^8$ light-emitting bacterial cells of E. coli via the femoral vein. When observed immediately after infection under the low light imager, bacterial colonization was visible in the liver region (FIG. 5). Three days later, while catheterized animals consistently demonstrated colonization of the heart with light emitting bacteria, control animals showed no sign of light emission from the heart (FIG. 6). To determine if low and undetectable levels of bacteria were present in the tissues, the heart, liver and spleen were excised from each animal and cultured overnight. The livers and spleens of the rats, which are organs that are directly involved in bacterial clearance, in both groups showed presence of light emitting bacteria. Strong light emission was detected in the catheterized heart in contrast to the control heart, which had complete absence of emitted light (FIG. 7). No bacteria were detected on the cultured catheters.